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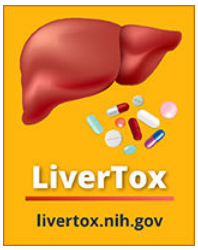

Ixekizumab

Updated: May 25, 2017.

OVERVIEW

Introduction

Ixekizumab is a humanized monoclonal antibody to interleukin-17A which acts as an antiinflammatory agent and is used to treat moderate-to-severe plaque psoriasis. Ixekizumab has not been linked to serum enzyme elevations during therapy or to instances of idiosyncratic acute liver injury.

Background

Ixekizumab (ix" ee kiz' ue mab) is a recombinant, humanized IgG4 monoclonal antibody to interleukin (IL)-17A, an important cytokine responsible for local release of proinflammatory mediators. The binding of the monoclonal antibody to the cytokine blocks its interaction with the receptor and thus decreases inflammatory pathways that are involved in immune mediated cell injury. Ixekizumab is considered an immunomodulatory and antiinflammatory agent and has been evaluated in several immune mediated diseases including rheumatoid arthritis, Crohn disease and psoriasis. In large clinical trials in moderate-to-severe plaque psoriasis, ixekizumab was shown to be beneficial in reducing symptoms and signs of the disease. Ixekizumab was approved for this use in the United States in 2016 and was the second IL-17A antagonist approved for this indication, the other being secukinumab [2015]. Ixekizumab is available in solution for injection in single dose prefilled syringes and autoinjectors of 80 mg [in one mL] under the brand Taltz. The recommended dose is 160 mg subcutaneously initially and then 80 mg every 2 weeks for 12 weeks and every 4 weeks thereafter. Side effects are not common, but can include injection site reactions, nausea, headache, upper respiratory tract and tinea infections. Rare, but potentially severe adverse reactions include neutropenia, severe bacterial infections, reactivation of tuberculosis, exacerbation of inflammatory bowel disease and immediate hypersensitivity reactions.

Hepatotoxicity

In large premarketing clinical trials, serum enzyme elevations were no more frequent with ixekizumab than with placebo injections and there were no instances of clinically apparent liver injury attributed to its use. Serum ALT elevations above 5 times the upper limit of normal were rare (<0.5%) and resolved without need of dose modification or discontinuation. Ixekizumab has had limited clinical use, but since its approval there have been no published case reports of liver injury attributed to ixekizumab therapy and no cases of reactivation of hepatitis B or autoimmune hepatitis, two possible hepatic complications of immunomodulatory monoclonal antibody therapy.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which ixekizumab might cause liver injury is unknown. Ixekizumab is a monoclonal antibody and, like other proteins, is metabolized into amino acids and is unlikely to have intrinsic toxicity. Because of its immunomodulatory activity, ixekizumab might induce an autoimmune reaction against hepatocytes, but this has not been shown.

Other immunomodulatory biologic agents used to treat severe psoriasis include adalimumab, brodalumab, certolizumab, efalizumab, etanercept, golimumab, infliximab, secukinumab and ustekinumab.

Drug Class: Dermatologic Agents, Psoriasis Agents; Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ixekizumab – Taltz®

DRUG CLASS

Dermatologic Agents, Psoriasis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Ixekizumab	1143503-69-8	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 25 May 2017

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999, well before the availability of most monoclonal antibody therapies).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents; mentions rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; ixekizumab is not specifically mentioned).

Kensky AM, Vincenti F, Bennett WM. Immunomodulators. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 1005-30.

(Textbook of pharmacology and therapeutics).

Burkhart C, Morrell D, Goldsmith L. Biologic agents. Dermatological pharmacology. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 1824-7.

(Textbook of pharmacology and therapeutics).

Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med 2012; 366: 1190-9. PubMed PMID: 22455413.

(Among 142 patients with psoriasis treated with ixekizumab [10, 25, 75 or 150 mg] or placebo for 16 weeks, clinical response rates were above 75% at high doses of ixekizumab but only 8% with placebo, and there were no serious adverse events or deaths while mean values of ALT and bilirubin "showed no change from baseline").

Gordon KB, Leonardi CL, Lebwohl M, Blauvelt A, Cameron GS, Braun D, Erickson J, et al. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. J Am Acad Dermatol 2014; 71: 1176-82. PubMed PMID: 25242558.

(Among 120 patients with psoriasis enrolled in an open label extension study after a controlled trial [Leonardi 2012], clinical response rates increased and were maintained through 52 weeks; among 15 serious adverse events, none were liver-related and most were considered unrelated to therapy).

Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, et al.; ERASURE Study Group; FIXTURE Study Group. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med 2014; 371: 326-38. PubMed PMID: 25007392.

(Among 1044 patients with plaque psoriasis treated with secukinumab [anti-IL-17A] or placebo in two large 52 week clinical trials, common side effects were nasopharyngitis, upper respiratory infection and diarrhea; no mention of ALT elevations or hepatotoxicity).

Genovese MC, Greenwald M, Cho CS, Berman A, Jin L, Cameron GS, Benichou O, et al. A phase II randomized study of subcutaneous ixekizumab, an anti-interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitors. Arthritis Rheumatol 2014; 66: 1693-704. PubMed PMID: 24623718.

(Among 348 patients with rheumatoid arthritis treated with ixekizumab [3, 10, 30, 80 or 180 mg] vs placebo for 12 weeks, clinical improvements were more frequent at the higher doses [39-54%] than with placebo [23-35%], while adverse event rates were similar; one patient on ixekizumab developed ALT elevations above 5 times ULN without bilirubin or Alk P elevations which resolved spontaneously without dose adjustment).

Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, et al.; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015; 386 (9993): 541-51. PubMed PMID: 26072109.

(Among 2570 patients with plaque psoriasis treated with etanercept, placebo or ixekizumab for 12 weeks, clinical improvements were more frequent with ixekizumab [78-90%] than etanercept [42-53%] or placebo [2-7%] as were adverse events, including injection site reactions and headache while "overall, we noted no clinically important changes from baseline in mean liver biochemical test results… in any treatment group").

Drugs for psoriasis. Med Lett Drugs Ther 2015; 57 (1470): 81-4. PubMed PMID: 26035749.

(Concise summary of current options for therapy of psoriasis including topical agents, phototherapy, oral systemic drugs, and biologic agents including secukinumab [anti-IL-17A], but not brodalumab [anti-IL-17A receptor] or ixekizumab [anti-IL-17A]; mentions that serious infections occurred in 1.2% of secukinumab treated patients; no mention of hepatotoxicity).

Genovese MC, Braun DK, Erickson JS, Berclaz PY, Banerjee S, Heffernan MP, Carlier H. Safety and efficacy of open-label subcutaneous ixekizumab treatment for 48 weeks in a phase II study in biologic-naive and TNF-IR patients with rheumatoid arthritis. J Rheumatol 2016; 43: 289-97. PubMed PMID: 26669919.

(Among 300 patients with rheumatoid arthritis treated with ixekizumab in a controlled trial [Genovese 2014] who were maintained on ixekizumab for 48 weeks in an open label extension study, clinical responses were maintained and adverse events included one instance of ALT elevations above 5 times ULN that resolved despite continuing therapy without dose adjustment).

Fragoulis GE, Siebert S, McInnes IB. Therapeutic targeting of IL-17 and IL-23 cytokines in immune-mediated diseases. Annu Rev Med 2016; 67: 337-53. PubMed PMID: 26565676.

(Review of the discovery and elucidation of the IL-17 and IL-23 cytokine pathways and their potential role as targets for therapy of immune mediated diseases).

Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, Reich K, et al.; UNCOVER-1 Study Group.; UNCOVER-2 Study Group.; UNCOVER-3 Study Group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med 2016; 375: 345-56. PubMed PMID: 27299809.

(Among 3866 patients with plaque psoriasis in controlled trials of ixekizumab who were given extended therapy for at least 60 weeks, clinical responses were maintained in 80% of patients, while serious adverse events included inflammatory bowel disease in 11 and neutralizing antibody in 19 patients [1.7%], but no mention of ALT elevations or hepatotoxicity).

Ixekizumab (Taltz)--a second IL-17A inhibitor for psoriasis. Med Lett Drugs Ther 2016; 58 (1494): 59-60. PubMed PMID: 27148922.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of ixekizumab shortly after its approval in the United States for plaque psoriasis; mentions common adverse effects, but does not mention ALT elevations or hepatotoxicity).

Saeki H, Nakagawa H, Nakajo K, Ishii T, Morisaki Y, Aoki T, Cameron GS, Osuntokun OO; Japanese Ixekizumab Study Group. Efficacy and safety of ixekizumab treatment for Japanese patients with moderate to severe plaque psoriasis, erythrodermic psoriasis and generalized pustular psoriasis: Results from a 52-week, open-label, phase 3 study (UNCOVER-J). J Dermatol 2017; 44: 355-62. PubMed PMID: 27726163.

(Among 92 Japanese patients with psoriasis treated with ixekizumab for 52 weeks, clinical responses occurred in 81% and adverse events in 89% including ALT elevations in 5 [6%]; no details provided, but there were no liver related serious adverse events).

Strober B, Leonardi C, Papp KA, Mrowietz U, Ohtsuki M, Bissonnette R, Ferris LK, et al. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: Etanercept comparisons and integrated data. J Am Acad Dermatol 2017; 76: 432-40 PubMed PMID: 27889292.

(Among 4209 patients with psoriasis enrolled in 7 clinical trials of ixekizumab and treated for 12-60 weeks, infections were more frequent with ixekizumab, but were mostly mild; no cases of active tuberculosis or invasive fungal infections occurred and no mention of ALT elevations or hepatoxicity).

Callis Duffin K, Bagel J, Bukhalo M, Mercado Clement IJ, Choi SL, Zhao F, Gill A, et al. Phase 3, open-label, randomized study of the pharmacokinetics, efficacy and safety of ixekizumab following subcutaneous administration using a prefilled syringe or an autoinjector in patients with moderate-to-severe plaque psoriasis (UNCOVER-A). J Eur Acad Dermatol Venereol 2017; 31: 107-13. PubMed PMID: 27500949.

(Among 204 patients with plaque psoriasis treated with ixekizumab using prefilled syringes vs autoinjectors, clinical response rates at 12 weeks were similar [89% vs 87%] as were adverse events [50% vs 45%]; no mention of ALT elevations or hepatotoxicity).

Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, Lin CY, et al.; SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017; 76: 79-87. PubMed PMID: 27553214.

(Among 417 patients with active psoriatic arthritis treated with adalimumab, placebo or ixekizumab [80 mg every 2 or 4 weeks] for 24 weeks, clinical response rates were highest with ixekizumab [60% vs 50% and 30%] as were adverse events rates [66% vs 64% vs 47%] including ALT elevations that occurred in 3-4% on ixekizumab vs none on placebo).